Help the Heart
An Update on GLP-1 Agonists and SGLT2 Inhibitors

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Objectives

1. Explain the advantages and disadvantages of GLP1 agonists and SGLT2 inhibitors

2. Review data from research studies about the potential benefits of GLP1 agonists and SGLT2 inhibitors

3. Outline placement of GLP-1 agonists and SGLT2 inhibitors in treatment algorithms
GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists

**MOA:** Activate the GLP-1 receptor and enhance glucose-dependent insulin release by the pancreatic beta-cells, decreases glucagon secretion, and slows gastric emptying.

![Diagram showing effects of GLP-1 receptor agonists on various tissues and organs](image)

*Figure 1* | Reported pleiotropic effects of GLP-1 or GLP-1 receptor agonists on various tissues and organs under experimental conditions. These effects do not necessarily represent physiological actions of the native incretin hormone, but have been observed in animal models, in vitro studies or in human studies using supraphysiological amounts of the peptide. Effects in the brain, heart, pancreas, skeletal muscle, blood vessels, kidney, fat cells, and liver are shown. Abbreviations: DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.

## GLP-1 Receptor Agonists

### Advantages
- Low risk of hypoglycemia
- Weight loss
- Strong A1c reduction
- Can be used in CKD (except exenatide)
- Possible CV benefits

### Disadvantages
- GI ADRs
- Expensive
- Injectable
- Pancreatitis
- Thyroid tumors
### Comparison of GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>A1c Reduction</th>
<th>Weight Loss</th>
<th>ADR Rates</th>
<th>Cost per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>30 or 50 mg SQ weekly</td>
<td>1%</td>
<td>1 kg</td>
<td>N: 11.1%  I: 18%</td>
<td>$480</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>0.75 or 1.5 mg SQ weekly</td>
<td>1.5%</td>
<td>2.5 kg</td>
<td>N: 12.4%, 21.1%[^a]  I: 0.5%</td>
<td>$625</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>0.6, 1.2, or 1.8 mg SQ weekly</td>
<td>1.5%</td>
<td>2.5 kg</td>
<td>N: 20%  I: 2%</td>
<td>$500, $750[^b]</td>
</tr>
<tr>
<td>Lixisenatide (Adlyxin®)</td>
<td>10 or 20 mg SQ daily</td>
<td>1%</td>
<td>2 kg</td>
<td>N: 25%  I: 4%</td>
<td>$600</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>5 mg or 10 mg SQ twice daily</td>
<td>1.5%</td>
<td>2.5 kg</td>
<td>N: 11.3%  I: 17.1%</td>
<td>$580</td>
</tr>
<tr>
<td>Exenatide (Byetta®)</td>
<td>2 mg SQ weekly</td>
<td>1%</td>
<td>2 kg</td>
<td>N: 8%, ≤44%[^c]  I: &lt;2%</td>
<td>$610</td>
</tr>
</tbody>
</table>

[^a]: First reported rate is for the 0.75 mg dose, second reported rate is for the 1.5 mg dose  
[^b]: First reported cost is for the 1.2 mg dose, second reported cost is for the 1.8 mg dose  
[^c]: First reported rate is for monotherapy, second reported rate is for add-on therapy

Adapted from Pharmacist’s Letter; Abbreviations: SQ=Subcutaneous, N=Nausea, I=Injection site reactions
**SGLT2 Inhibitors**

**Sodium Glucose Co-Transporter 2 Inhibitors**

**MOA:** reduces the reabsorption of glucose from the renal tubules and therefore increases the excretion of urinary glucose

### SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk of hypoglycemia</td>
<td>UTI and genital fungal infection ADRs</td>
</tr>
<tr>
<td>Oral medication</td>
<td>Expensive</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Lowers BP</td>
<td>Cannot be used in CKD (higher stages)</td>
</tr>
<tr>
<td></td>
<td>Less efficacious than insulin and GLP-1 receptor agonists</td>
</tr>
<tr>
<td></td>
<td>Bone fractures (canagliflozin)</td>
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</tbody>
</table>
# Comparison of SGLT2 Inhibitors

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<th>A1c Reduction</th>
<th>Weight Loss</th>
<th>ADR Rates</th>
<th>Cost per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>100 or 300 mg PO daily</td>
<td>1%</td>
<td>2.8 kg</td>
<td>GMI: 11%, 4%&lt;sup&gt;a&lt;/sup&gt; UTI: 5%</td>
<td>$512</td>
</tr>
<tr>
<td>(Invokana®)</td>
<td></td>
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<tr>
<td>Dapagliflozin</td>
<td>5 or 10 mg PO daily</td>
<td>1.2%</td>
<td>3 kg</td>
<td>GMI: 7%, 2.7%&lt;sup&gt;b&lt;/sup&gt; UTI: 5%</td>
<td>$516, $411&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Farxiga®)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Empaglifazin</td>
<td>10 or 25 mg PO daily</td>
<td>0.75%</td>
<td>1.8 kg</td>
<td>GMI: 6%, 2.4%&lt;sup&gt;c&lt;/sup&gt; UTI: 8.5%</td>
<td>$516</td>
</tr>
<tr>
<td>(Jardiance®)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: PO=By mouth, GMI=genital mycotic infection, UTI=urinary tract infection

<sup>a,b,c</sup> First reported rate is for females, second reported rate is for males

<sup>d</sup> First reported cost is for the 5 mg dose, second reported cost is for the 10 mg dose
LEADER Trial
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Methodology

• Liraglutide vs. placebo
  - Liraglutide 1.8 mg (or max tolerated dose) in addition to standard of care

• Double-blind, multicenter, randomized control study

• Population: type 2 diabetes at high risk of CV disease

• Follow-up: 1, 3, 6 months and then every 6 months

LEADER

Outcomes

Primary Outcome

• Composite outcome, time-to-event analysis: death from CV causes, nonfatal MI, or nonfatal stroke

Exploratory outcomes

• Death from any cause
• Composite of renal and retinal microvascular complications
• Neoplasms
• Pancreatitis
LEADER

Results

• 9340 patients (4668 liraglutide vs 4672 placebo)
• Median exposure time: 3.5 years
• Median follow-up time: 3.8 years

LEADER

Results (continued)

• A1c reduction: ~0.4%
• Weight loss: ~2.3 kg
• SBP reduction: ~1.2 mmHg
• Composite renal or retinal microvascular events lower in liraglutide group: 355 vs 416 patients (hazard ratio, 0.84; 95% CI, 0.73 to 0.97; $P = 0.02$)
• Severe hypoglycemia lower in liraglutide group: 114 vs 153 patients (hazard ratio, 0.84; 95% CI, 0.73 to 0.97; $P = 0.02$)
• Adverse events leading to discontinuation: more common in liraglutide (mostly GI effects)
• Acute pancreatitis and neoplasms: non-significant differences
LEADER

Conclusion

• Liraglutide had lower risk of primary outcome: CV death, nonfatal MI, nonfatal stroke and lower risks of death from CV causes, death from any cause and microvascular events compared to placebo
  • Number needed to treat (NNT): 66 to prevent one event in 3 years for primary outcome and 98 for death from any cause
EMPA-REG OUTCOME Trial
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Methodology

- Empagliflozin vs placebo
  - Empagliflozin 10 mg or 25 mg once daily in addition to standard of care
- Double-blind, multicenter, randomized control study
- Population: type 2 diabetes with established CV disease
- Follow-up: 1 month, 3 month, 1 year, and then yearly

EMPA-REG OUTCOME

Outcomes

Primary Outcome

- Composite outcome, analyzed as a pooled empagliflozin group: death from CV causes, nonfatal MI, or nonfatal stroke

Secondary Outcome

- Composite outcome: primary outcome plus hospitalization for unstable angina
EMPA-REG OUTCOME

Results

- 7020 patients (2342 empagliflozin 20 mg, 2345 empagliflozin 10 mg, and 2333 placebo)
- Median exposure time: 2.6 years
- Median follow-up time: 3.1 years
EMPA-REG OUTCOME

Results (continued)

• Secondary outcome: 12.8% vs 14.3% in the placebo group (hazard ratio, 0.89; 95% CI, 0.78 to 1.01; \( P<0.001 \) for noninferiority and \( P = 0.08 \) for superiority)

• Increased genital infections: 6.4% vs 1.8% (\( p<0.001 \))

• A1c reduction: \(~0.3\%\)

• SBP reduction: \(~4\) mmHg

• Weight loss: \(~2\) kg

• Diabetic ketoacidosis: non-significant difference

• Hypoglycemia, acute renal failure and bone fractures: no difference
EMPA-REG OUTCOME

Conclusion

• Empagliflozin had lower risk of composite CV outcome and death from any cause compared to placebo
  • Similar for both doses studied

• Number needed to treat (NNT): 39 patients would need to be treated for 3 years to provide benefit in these outcomes
Other Published CV Outcome Trials

• **ELIXA**: lixisenatide (once daily injection) showed CV safety but no significant CV benefit

• **SUSTAIN-6**: semaglutide (once weekly injection, not yet approved) significantly reduces CV risk
  • More support for class effect for long acting GLP-1 agonists
CV Outcome Trials

• Observed benefits and risks may not apply to lower risk patients
• Do not know if reduction in CV outcomes is a class effect
• Benefit is not related to reduction in plasma glucose
  • Liraglutide: longer metabolic effect with reduction in atherosclerosis progression
  • Empagliflozin: immediate hemodynamic actions such as decrease in blood pressure
Question #1

What are the most likely mechanisms contributing to the reduction in CV mortality by empagliflozin?

A. Lowered plasma glucose concentration
B. Weight loss
C. Decrease in blood pressure
D. Direct effect on the myocardium
Question #1

What are the most likely mechanisms contributing to the reduction in CV mortality by empagliflozin?

A. Lowered plasma glucose concentration
B. Weight loss
C. Decrease in blood pressure
D. Direct effect on the myocardium
DURATION-8 Trial
Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy

Methodology

• Multi-center, double-blind, randomized study

• Population: Inadequate glycemic control (A1c 8-12%) despite metformin monotherapy (≥1500 mg/day)
  • Exenatide 2 mg weekly + dapagliflozin 10 mg daily or each alone with matched placebos

• Primary Endpoint: change in A1c from baseline at 28 weeks

• Secondary Endpoints: fasting glucose, 2hr post-prandial glucose, proportion of patients with weight loss of ≥5%, and change in systolic blood pressure

*Lancet Diabetes Endocrinol. 2016 Dec;4(12):1004-1016*
DURATION-8

Results

• 695 patients (231 exenatide+dapagliflozin, 231 exenatide alone, 233 dapagliflozin alone)
  • Exenatide plus dapagliflozin significantly reduced A1c from baseline to week 28 compared with exenatide alone (–0.4% [95% CI –0.6 to –0.1]; \( p=0.004 \)) or dapagliflozin alone (–0.6% [–0.8 to –0.3]; \( p<0.001 \))
  • Exenatide plus dapagliflozin was significantly superior to either drug alone for all secondary efficacy endpoints
DURATION-8

Conclusion

Co-initiation of exenatide and dapagliflozin improved various glycemic measures and cardiovascular risk factors in patients with type 2 diabetes inadequately controlled by metformin monotherapy

• The dual treatment regimen was well tolerated, with the expected safety profile for this combination

• Unclear if would obtain similar results from sequential addition of agents rather than simultaneous addition
2017 ADA Guidelines

Start with Monotherapy unless:

- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

Monotherapy

<table>
<thead>
<tr>
<th>Efficacy*</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td></td>
<td></td>
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<tr>
<td>Lactic Ac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient & disease-specific factors):

Dual Therapy

<table>
<thead>
<tr>
<th>Efficacy*</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient & disease-specific factors):

Triple Therapy

<table>
<thead>
<tr>
<th>Efficacy*</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Lactic Ac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient: (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy  
(See Figure 8.2)
2017 AACE Guidelines

**Entry A1C < 7.5%**

- **MONOTHERAPY***:
  - Metformin
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - TZD
  - AGi
  - SU/GLN

If not at goal in 3 months proceed to Dual Therapy

**Entry A1C ≥ 7.5%**

- **DUAL THERAPY***:
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - TZD
  - Basal Insulin
  - Colesvelam
  - Bromocriptine QR
  - AGi
  - SU/GLN

If not at goal in 3 months proceed to Triple Therapy

**Entry A1C > 9.0%**

- **SYMPTOMS**
  - NO
    - DUAL Therapy
    - OR
    - TRIPLE Therapy
  - YES
    - INSULIN ± Other Agents

**ADD OR INTENSIFY INSULIN**
Refer to Insulin Algorithm

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

**LEGEND**
- ✓ Few adverse events and/or possible benefits
- ! Use with caution

*MAYO CLINIC HEALTH SYSTEM

Endocr Pract. 2017, 236

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Positioning GLP-1 Agonists and SGLT2 Inhibitors in Diabetes Management

• 2017 ADA guidelines mentions the results of the EMPA-REG OUTCOME and LEADER trials

• FDA added indication for empagliflozin to reduce risk of CV death in adults with type 2 diabetes and established CV disease

• Positive attributes: efficacy in A1c reduction, weight loss, BP reduction, low risk of hypoglycemia, good safety profile, improvement in CV outcomes
Positioning GLP-1 Agonists and SGLT2 Inhibitors in Diabetes Management

- Consider use early in history of diabetes with:
  - Age: ≥60
  - Established ASCVD
  - High CV risk

- Ultimate place in guidelines to be determined by ongoing CV and renal trials

- No head-to-head comparison trials
Question #2

In which patient may a GLP-1 agonist be added for dual therapy?

A. Patient with pancreatitis
B. Patient with chronic kidney disease
C. Patient with a thyroid tumor
D. Patient unable to self-inject
Question #2

In which patient may a GLP-1 agonist be added for dual therapy?

A. Patient with pancreatitis
B. Patient with chronic kidney disease
C. Patient with a thyroid tumor
D. Patient unable to self-inject
Question #3
Which patient would be the best candidate for a SGLT2 inhibitor to be added for dual therapy?

A. Age 50, history of myocardial infarction, history of recurrent urinary tract infections

B. Age 65, congestive heart failure, chronic kidney disease

C. Age 50, congestive heart failure, history of diabetic ketoacidosis

D. Age 65, history of myocardial infarction, unable to self-inject
Question #3

Which patient would be the best candidate for a SGLT2 inhibitor to be added for dual therapy?

A. Age 50, history of myocardial infarction, history of recurrent urinary tract infections

B. Age 65, congestive heart failure, chronic kidney disease

C. Age 50, congestive heart failure, history of diabetic ketoacidosis

D. Age 65, history of myocardial infarction, unable to self-inject
Future Studies

• CV outcomes
  • CANVAS: canagliflozin
  • DECLARE-TIMI 58: dapagliflozin
  • EXSCEL: exenatide
  • REWIND: dulaglutide
New Agents in Clinical Trials

• Daily Oral GLP-1 agonist
  • semaglutide
• Once-monthly Injectable GLP-1 agonists
  • Exenatide
  • Epeglenatide
Final Takeaways

• GLP-1 agonists and SGLT2 inhibitors have their own advantages and disadvantages

• CV benefit of liraglutide and empagliflozin has been shown in studies
  • Still unclear if this is a drug class effect
  • Consider their use early in history of diabetes and in patients with CV disease/high risk of CV events

• Place in therapy to be determined after future studies are complete
  • Utilize patient specific considerations to choose add-on therapies
References


Questions & Discussion

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